Occupational Exposure to Diesel Exhaust and Lung Cancer: A Meta-Analysis

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ABSTRACT

Objectives. We undertook a meta-analysis of epidemiological studies investigating the relationship between occupational diesel exhaust exposure and lung cancer.

Methods. Thirty of 47 studies initially identified as potentially relevant met specified inclusion criteria. We extracted or calculated 39 independent estimates of relative risk and derived pooled estimates of risk for all studies and for numerous study subsets by using a random-effects model. We also examined interstudy heterogeneity by using linear metaregressions.

Results. There was substantial heterogeneity in the pooled risk estimates for all studies combined and for most subsets. Several factors consistent with higher study quality, however, contributed to increased pooled estimates of risk and lower heterogeneity, including (1) adjustment for confounding by cigarette smoking and other covariates, (2) having a lower likelihood of selection bias, and (3) having increased study power.

Conclusion. This analysis provides quantitative support for prior qualitative reviews that have ascribed an etiologic role to occupational diesel exhaust exposure in lung cancer induction. Among study populations most likely to have had substantial exposure to diesel exhaust, the pooled smoking-adjusted relative risk was 1.47 (95% confidence interval = 1.29, 1.67). (*Am J Public Health.* 1999;89:1009–1017)

Numerous epidemiological investigations have examined whether occupational exposure to diesel exhaust is associated with lung cancer. Although several recent reviews have concluded that the evidence is consistent with a causal relationship, others have not.[1–6] A meta-analysis cannot prove or disprove causality per se; however, it can explore the basis for differences among studies and in so doing provide evidence bearing on causal inference.

Materials and Methods

Identification and Selection of Studies

Electronic searches were conducted with MEDLINE,[7] TOXLINE,[8] and NIOSHTIC[9] to identify epidemiological studies published from 1975 through 1995 purporting to examine occupational exposure to diesel exhaust in relation to lung cancer. This search was supplemented with additional articles cited in those identified electronically. We excluded from consideration studies focusing on occupations involving mining because of potential confounding by radon, arsenic, and silica, as well as possible interactions between cigarette smoking and exposure to these substances in lung cancer induction.[10–12] Since studies of miners often indicate higher relative risks for lung cancer than those considered in this meta-analysis, this was a conservative exclusion.[12–15]

Forty-seven studies were identified as potentially relevant.[13–59] Studies were selected for inclusion on the basis of the following criteria. (1) Estimates of relative risks (including standardized mortality ratios and odds ratios) and their standard errors must be reported or derivable from the information presented. (2) Studies must have allowed for an adequate latency period (≥10 years) for the development of lung cancer after the onset of exposure. Studies lacking information for estimating latency were also included if the interval between the study period and the target industry's transition to diesel was long enough that a sufficient latency period had elapsed for much, if not all, of the cohort. (3) There should be no obvious bias resulting from incomplete case ascertainment in follow-up studies—for example, by excluding cases of lung cancer arising in retirees. (4) Studies must be independent. If multiple studies were conducted in the same population, then the study that best met the other criteria was selected, and the others were excluded as redundant.

Data Extraction

No studies reported standard errors; several did not report confidence intervals (or even relative risks in 2 instances). We calculated risk estimates and approximate 95% confidence intervals by Woolf's and Byar's formulas; standard errors were estimated from confidence intervals or with test-based methods.[60–62]

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Editor's Note. Please see related editorial by Stayner (p 991) in this issue.

All risk estimates and standard errors were logarithmically transformed prior to analysis.

If a study reported effects associated with several levels or durations of exposure, the effect reported for the highest level or longest duration of exposure was used. However, in instances where multiple strata with 20 or more years of exposure were reported, a pooled effect measure was calculated with the general variance-based method.[60] If estimates for several occupational subsets were reported, the most diesel-specific occupation or exposure group was selected—for example, truck drivers instead of all professional drivers. Where both crude and adjusted risk estimates were presented, only the latter were used. Several risk estimates were extracted from 6 studies reporting results for multiple, mutually exclusive diesel-related occupational subgroups.[19,23,36,43,54,55] We used estimates from the nested case–control study by Gustavsson et al.[33] rather than the retrospective cohort investigation of the same population, because the latter grouped mesotheliomas with lung cancer. Of 2 investigations of dockworkers, the earlier study by Gustafsson et al.[32] was included in order to incorporate the experience of the entire cohort, as opposed to the more limited nested case–control analysis by Emmelin et al.[28]

Analysis

Given the multifactorial etiology of lung cancer, the variability of exposure patterns and durations, and the different biases, confounders, and effect modifiers across studies, we considered a random-effects model to be more appropriate than a fixed-effects model for deriving pooled risk estimates; we used that of DerSimonian and Laird, which allows for heterogeneity in risk estimates across studies.[63] Under this model, a pooled relative risk estimate is calculated as a weighted average of the risks reported in each study, with the weight equal to the inverse of the sum of the among-study and within-study variances. We evaluated the significance of the among-study variance with the Q statistic, which has a χ^2 distribution with degrees of freedom equal to 1 less than the number of studies pooled. A low P value for this statistic indicates the presence of heterogeneity, which undermines the validity of the pooled estimates.[63,64]

Because significant heterogeneity was clearly evident in the pooled relative risk estimates for all studies combined, we evaluated potential sources of heterogeneity by subset analysis and linear metaregressions. Indicator variables were created to characterize study design, occupational category, source of reference population, latency (greater than 10 years or undefined), duration of exposure (with intervals of 10 and 20 years), method of identifying cases, method of ascertaining occupation, year of publication, location (North America or Europe), number of covariates controlled for in the analysis, and presence of a clear healthy-worker effect (manifested as significantly lower-than-expected all-cause mortality).

For subset analysis, we grouped the data by study characteristics, calculating subgroup-specific pooled relative risks. A factor was considered to be an important source of heterogeneity if stratification on that factor markedly affected the heterogeneity of the stratum-specific estimates of effect (e.g., if the P value of the Q statistic increased from less than .01 to greater than .10). Regression of the estimated relative risks on the indicator variables, weighted by the inverse of the studies' squared standard errors, allowed evaluation of heterogeneity across several study characteristics simultaneously.[60] A "metacoefficient" for a given indicator variable estimated the difference between the average coefficient for the group of studies subsumed by that variable and the average coefficient for the remaining studies.[60]

Sensitivity analyses included (1) deleting studies in which exposure to diesel exhaust was not distinguishable from exposure to exhaust from conventional internal combustion engines[17–20,36,57] and (2) substituting excluded "redundant" studies for those that had been included.[13,22,25,28,34,51,53] Influence analyses that involved reestimation of the pooled relative risk while dropping 1 study at a time were also conducted to examine whether any studies disproportionately influenced the results. Publication bias refers to the increased likelihood of publication of manuscripts containing statistically significant results compared with reports with nonsignificant or null results; such bias may distort pooled risk estimates. To examine potential publication bias, we plotted the logarithm of the estimates of relative risk against the inverse of the studies' standard errors; in the absence of publication bias, the plot should resemble an inverted funnel with the vertex over the central effect estimate.[64]

Microsoft Excel Version 5.0 (Microsoft Corporation, Redmond, Wash) and PC-SAS Version 6.10 (SAS Institute, Inc, Cary, NC) were used to conduct the statistical analysis.

Results

Thirty studies, contributing a total of 39 effect estimates, met the inclusion criteria (Tables 1 and 2). As shown in Table 3, the pooled relative risk for lung cancer from all 39 risk estimates combined showed evidence of serious heterogeneity.

Subset analyses identified several sources of heterogeneity (Table 3). A modestly higher pooled risk estimate was derived for the subset of case–control studies, which, unlike the cohort studies, showed little evidence of heterogeneity. Dividing the cohort studies into subsets with and without a healthy-worker effect markedly reduced the degree of heterogeneity in the group without a healthy-worker effect and increased the magnitude of the pooled relative risk estimate. Pooled estimates for cohort studies derived from regional/state or national lung cancer rates as the basis for comparison demonstrated greater heterogeneity and lower relative risk estimates than did those for studies using a reference population of internal controls or another occupationally active cohort. Not surprisingly, 7 of the 8 cohort studies composing the group with a clear healthy-worker effect used national rates for comparison.

Adjustment for cigarette smoking was a major source of heterogeneity. The 12 studies (20 risk estimates) that adjusted for smoking showed little evidence of heterogeneity and a modestly higher pooled estimate than the 18 studies (19 risk estimates) that did not. Subset analyses by specific occupations demonstrated pooled relative risk estimates with little evidence of heterogeneity for truck drivers, professional drivers/general transportation operatives, and grouped diesel-exposed occupations. Figure 1 depicts pooled relative risk estimates for all studies and for several study subsets.

Asbestos exposure was less common than cigarette smoking in these study populations, and there was no evidence of heterogeneity among the 5 studies that adjusted for this potential confounder (relative risk [RR] = 1.47; 95% confidence interval [CI] = 1.30, 1.67). However, because 4 of these studies also adjusted for smoking, the separate influences of these 2 factors cannot be disentangled. For studies that controlled for 3 or more covariates (all but 1 of which included cigarette smoking), the pooled estimate for relative risk was 1.43 (95% CI = 1.29, 1.57), with little evidence of heterogeneity, while for those that controlled for fewer than 3, the pooled estimate was lower (RR = 1.26; 95% CI = 1.13, 1.40) and contained substantial heterogeneity.

Stratifying the data on other study characteristics, including region, source population, latency, and method of job ascertainment, yielded point estimates of pooled relative risks ranging from 1.00 to 1.70, most of which were statistically significant but were also characterized by the presence of heterogeneity (data not shown).

TABLE 1—Studies Included in Meta-Analysis of Diesel Exhaust Exposure and Lung Cancer

Study (Year)	Design	Location	Occupation or Exposure Group	Smoking Adjusted	No. of Lung Cancer Cases	RR	95% CI
Ahlberg et al. (1981)[16]	Cohort	Europe	Truck drivers	No	154	1.33	1.13, 1.56
Balarajan and McDowall (1988)[17]	Cohort	Europe	Truck drivers	No	280	1.59	1.00, 2.53[a]
Bender et al. (1989)[18]	Cohort	North America	Highway maintenance	No	54	0.69	0.52, 0.90
Benhamou et al. (1988)[19]	Case–control	Europe	Professional drivers	Yes	128	1.42	1.07, 1.89
	Case–control	Europe	Mechanics	Yes	65	1.06	0.73, 1.54
Boffetta et al. (1988)[23]	Cohort	North America	Truck drivers	Yes	48	1.24	0.93, 1.66
	Cohort	North America	Railroad workers	Yes	14	1.59	0.94, 2.69
	Cohort	North America	Heavy equipment operators	Yes	5	2.60	1.12, 6.06
Boffetta et al. (1990)[21]	Case–control	North America	Probable DE exposure ≥ 30 y	Yes	17	1.49	0.72, 3.11
Buiatti et al. (1985)[20]	Case–control	Europe	Transportation general	Yes	376	1.1	0.7, 1.6
Coggon et al. (1984)[24]	Case–control	Europe	DE-exposed group	No	32	1.1	0.7, 1.8
Damber and Larsson (1987)[14]	Case–control	Europe	Professional drivers	Yes	37	1.2	0.6, 2.2
Edling et al. (1987)[27]	Cohort	Europe	Bus drivers	No	5	0.69[b]	0.2, 1.6[b]
Garshick et al. (1987)[29]	Case–control	North America	Railroad workers ≥ 20 y[c]	Yes	117[f]	1.55	1.09, 2.21
Garshick et al. (1988)[30]	Cohort	North America	Railroad workers ≥ 15 y[c]	No	Not given	1.82	1.30, 2.55
Guberan et al. (1992)[31]	Cohort	Europe	Professional drivers	No	77	1.50	1.23, 1.81
Gustafsson et al. (1986)[32]	Cohort	Europe	Dock workers	No	70	1.32	1.05, 1.66
Gustavsson et al. (1990)[33]	Nested case–control	Europe	Bus garage workers[d]	No	15	1.49[d]	1.25, 1.77[d]
Hansen (1993)[35]	Cohort	Europe	Truck drivers	No	76	1.6	1.26, 2.0
Hayes et al. (1989)[36]	Case–control	North America	Truck drivers ≥ 10 y	Yes	112	1.5	1.1, 2.0
	Case–control	North America	Bus drivers ≥ 10 y	Yes	24	1.7	0.8, 3.4
	Case–control	North America	Mechanics (excluding auto) ≥ 10 y	Yes	18	2.1	0.9, 5.2
	Case–control	North America	Heavy equipment operators ≥ 10 y	Yes	10	2.1	0.6, 7.1
Howe et al. (1983)[37]	Cohort	North America	Railroad workers probably exposed	No	279	1.35	1.13, 1.61[a]
Lerchen et al. (1987)[15]	Case–control	North America	DE grouped	Yes	7	0.6	0.2, 1.6
Magnani et al. (1988)[41]	Death certificate study	Europe	DE grouped	No	379	0.97	0.94, 0.99
Menck and Henderson (1976)[43]	Cohort	North America	Truck drivers	No	109	1.65	1.13, 2.40[a]
	Cohort	North America	Mechanics (excluding auto)	No	46	3.32	1.35, 8.18[a]
Nokso-Koivisto and Pukkala (1994)[46]	Cohort	Europe	Railroad workers	No	230	0.90[d]	0.79, 1.04[d]
Pfluger and Minder (1994)[47]	Case–control	Europe	Professional drivers	Yes	284	1.48	1.30, 1.68
Rafnsson and Gunnarsdottir (1991)[49]	Cohort	Europe	Truck drivers ≥ 30 y	No	<24[f]	2.32	0.85, 5.04
Rushton et al. (1983)[50]	Cohort	Europe	Bus garage workers/mechanics	No	102	1.01	0.82, 1.22[b]
Siemiatycki et al. (1988)[52]	Case–control	North America	Diesel exhaust grouped	Yes	70	1.1	0.8, 1.5[e]
Steenland et al. (1990)[54]	Case–control	North America	Truck drivers ≥ 18 y	Yes	213	1.55	0.97, 2.47
	Case–control	North America	Truck mechanics ≥ 18 y	Yes	16	1.50	0.59, 3.40
Swanson et al. (1993)[55]	Case–control	North America	Heavy truck drivers ≥ 20 y	Yes	137	2.44[d]	1.43, 4.16[d]
	Case–control	North America	Railroad workers ≥ 10 y	Yes	49	2.46[d]	1.24, 4.87[d]
Wegman and Peters (1978)[57]	Case–control	North America	Transportation equipment operators	No	9	2.39[b]	0.71, 8.05[b]
Wong et al. (1985)[59]	Cohort	North America	Heavy equipment operators ≥ 20 y	No	163	1.07	1.00, 1.15[a]

Note. DE = diesel exhaust; RR = relative risk; CI = confidence interval.
[a]Calculated from *P* value.
[b]Calculated from data presented in publication.
[c]Risk estimates excluding shop workers.
[d]Pooled risk estimates from 2 racial or duration categories.
[e]90% confidence intervals originally presented within study.
[f]Exact number of cases for stratum analyzed not available.

Subgroup analysis based on duration of exposure, typically measured as years of employment, was hampered by the lack of duration-specific risk estimates in 19 studies. Among the different duration strata, there remained considerable heterogeneity and no clear evidence of an exposure–response trend. However, by stratifying the smoking-adjusted risk estimates on duration of exposure, a modest exposure–response relationship was suggested by the pooled risk estimates (for <10 years, RR = 1.39 [CI = 1.19, 1.63]; for ≥10 years, RR = 1.64 [CI = 1.40, 1.93]). Also, within the only occupational subgroup with sufficient numbers to identify duration-specific estimates (truck drivers), there was modest evidence of such a trend, although this was based on few studies per stratum (for <20 years, pooled RR = 1.51 [95% CI = 1.18, 1.95]; for ≥20 years, pooled RR = 2.41 [95% CI = 1.53, 3.81]).

Additional stratification by both occupation and adjustment for smoking was conducted. This resulted in a marked reduction in heterogeneity among smoking-adjusted studies of railroad workers, mechanics/garage workers, heavy equipment operators/dockworkers, and the general diesel exhaust–grouped occupations (data not shown). Substantial heterogeneity remained in most industry subsets that were not adjusted for smoking.

TABLE 2—Studies Excluded From Meta-Analysis of Diesel Exhaust Exposure and Lung Cancer

Study (Year)	Reason for Exclusion	Occupation or Exposure Group
Boffetta et al. (1989)[22]	Redundant study/ duplicate report	Grouped DE exposure
Burns and Swanson (1991)[13]	Redundant study	General population
Damber and Larsson (1985)[25]	Redundant study	Professional drivers
Decoufle et al. (1977)[26]	Inadequate latency	Professional drivers
Emmelin et al. (1993)[28]	Redundant study	Dock workers
Hall and Wynder (1984)[34]	Redundant study	Grouped DE exposure
Kaplan (1959)[38]	Inadequate latency	Railroad workers
Kauppinen et al. (1993)[39]	Inadequate latency	Woodworkers
Luepker and Smith (1978)[40]	Excluded retirees	Truck drivers
Maizlish et al. (1988)[42]	Excluded retirees	Bus drivers
Milne et al. (1983)[44]	Inappropriate effect measure	Highway maintenance
Netterström (1988)[45]	Inadequate latency	Truck and bus drivers
Raffle (1957)[48]	Excluded most retirees	Bus and trolley
Schenker et al. (1984)[51]	Redundant study	Railroad workers
Siemiatycki (1990)[53]	Redundant study	Grouped DE exposure
Waller (1981)[56]	Excluded retirees	Bus company
Williams et al. (1977)[58]	Inadequate data presentation	Railroad workers and truck drivers

Note. DE = diesel exhaust.

Sensitivity analyses did not substantially alter the results of the subset analyses. Substituting redundant studies for those originally included did not markedly change the pooled relative risk estimates. Rerunning some subgroup analyses, omitting those in which it was not possible to distinguish diesel from internal combustion engine exhaust exposures,[17–20,36,57] had little effect on the overall pooled estimates or on those derived from specific occupational subgroups (Table 3, italicized estimates). Similarly, influence analyses of occupational subgroups with 5 or more studies (truckers, railroad workers, mechanics/garage workers, and professional drivers/general transportation operatives) did not change the pooled estimates much, regardless of which study was excluded, with 1 exception. After exclusion of the risk estimate from the study of Nokso-Koivisto and Pukkala,[46] the pooled relative risk for railroad workers increased to 1.50 (95% CI = 1.31, 1.71), with little evidence of heterogeneity (Q statistic = 4.729, $df = 4$, $P = .316$).

Results of the initial bivariate weighted linear metaregressions tended to confirm the subset analyses, identifying statistically significant associations ($P < .05$) between the coefficients for all studies combined and several study characteristics, including presence of a healthy worker effect, case–control design, adjustment for smoking, several occupational subgroups, and 2 reference population categories (internal or other occupationally active controls and national mortality rates). Because the study design metacoefficient was highly significant ($P < .001$), further analysis was conducted separately for case–control and cohort studies.

In multivariate modeling based on the results of separate bivariate analyses for cohort and case–control studies, several study characteristics were strongly intercorrelated, which limited the combinations of variables that could be used simultaneously. Among cohort studies, the variables that consistently remained significant in a variety of models included the presence of a healthy worker effect (metacoefficient = –0.320, $P = .001$) and study size (metacoefficient = 0.449, $P = .036$). For the case–control studies, the model with the best fit (adjusted $R^2 = 0.44$) included publication in 1989 or later and exposure duration of 10 or more years, with metacoefficients of 0.300 ($P = .007$) and 0.275 ($P = .03$), respectively.

The funnel plot (Figure 2) revealed no systematic relationship between study size and magnitude of risk, although there is a lower density of studies in the lower left, indicating fewer small, statistically insignificant studies. However, estimates from the smaller studies spanned the entire range of relative risk estimates.

Discussion

Although substantial heterogeneity existed in the initial pooled estimates, stratification on several factors substantially reduced heterogeneity, producing subsets of studies with increased relative risk estimates that persisted through various influence and sensitivity analyses. Major sources of heterogeneity identified included control for confounding, selection bias, and exposure patterns characteristic of different occupational categories.

In studies that adjusted for confounding by cigarette smoking, not only did the positive association between diesel exhaust exposure and lung cancer persist but the pooled risk estimate showed a modest increase, with little evidence of heterogeneity. Although the metacoefficient representing adjustment for cigarette smoking exercised a positive effect on the pooled risk estimates in bivariate regressions of all studies, this study characteristic did not emerge as a significant source of heterogeneity among the case–control studies, presumably because most adjusted for this factor (11 of 14 studies, accounting for 17 of 20 estimates). Since cigarette smoking dwarfs all other known risk factors for lung cancer, it is likely that adjustment for smoking is the principal factor responsible for the relative homogeneity of the case–control study estimates, although other aspects of the study design may also have played a role.

Because cigarette smoking is such a strong risk factor for lung cancer, misclassification of this exposure could result in residual confounding.[65,66] Because most of the information about subjects' smoking came from proxy respondents, some misclassification undoubtedly occurred.[67,68] However, the impact of any consequent residual confounding is likely to have been weakened by the more extensive measurement error related to assessment of exposure to diesel exhaust.[65] In addition, the pooled estimates for smoking-adjusted studies by occupation were modestly greater than or virtually the same as those that were not adjusted for smoking in all occupational groups except mechanics/garage workers. Although these trends are based on small numbers of reports, greater precision in the measurement of this confounder would be unlikely to eliminate the increased diesel-associated relative risks.

Diet may also confound the diesel–lung cancer association, and it was not controlled for in the studies included in this analysis. Long-haul truck drivers consume more restaurant meals than the general population, resulting in a lower intake of anticarcinogenic micronutrients,[69,70] but diet would probably not be an important confounder in studies of other occupations, particularly those using internal or other occupationally active reference populations.

Selection bias also helps explain the findings of the case–control vs the cohort studies. The healthy worker effect emerged as a major source of heterogeneity among the cohort studies, in both the subset analyses and the metaregressions. Although it can also

TABLE 3—Studies of Occupational Diesel Exhaust Exposure and Lung Cancer: Pooled Estimates of Relative Risk Based on Random-Effects Model

Group (No. of Risk Estimates/No. of Studies)	Q Statistic (*df*, *P*)	Pooled RR	95% CI
All studies			
(n = 39/30)	214.58 (38, .001)	1.33	1.21, 1.46
(n = 29/24)	*184.83 (28, <.001)*	*(1.35)*	*1.22, 1.49*
By study design			
Cohort			
(n = 18/15)	77.655 (17, <.001)	1.29	1.14, 1.47
(n = 16/13)	*61.122 (15, <.001)*	*(1.33)*	*1.18, 1.51*
With clear healthy worker effect			
(n = 8/8)	29.284 (7, <.001)	1.06	0.92, 1.23
(n = 6/6)	*16.687 (5, .005)*	*(1.10)*	*0.96, 1.25*
Without clear healthy worker effect (n = 10/7)	11.190 (9, .263)	1.52	1.36, 1.71
Case–control			
(n = 20/14)	19.248 (19, .441)	1.44	1.33, 1.56
(n = 12/10)	*12.823 (11, .305)*	*(1.46)*	*1.31, 1.63*
By adjustment for smoking			
Smoking adjusted			
(n = 20/12)	20.241 (19, .380)	1.43	1.31, 1.57
(n = 13/9)	*14.519 (12, .269)*	*(1.47)*	*1.29, 1.67*
Smoking not adjusted			
(n = 19/18)	129.101 (18, <.001)	1.25	1.12, 1.39
(n = 16/15)	*115.961 (15, <.001)*	*(1.27)*	*1.14, 1.43*
By occupation			
Truck drivers (n = 9/9)	8.369 (8, .398)	1.47	1.33, 1.63
Railroad workers (n = 6/6)	30.902 (5, <.001)	1.45	1.08, 1.93
Mechanics/garage workers (n = 6/6)	14.968 (5, .010)	1.35	1.03, 1.78
Heavy equipment operators/dockworkers (n = 4/4)	8.016 (3, .046)	1.28	0.99, 1.66
Professional drivers/transportation operatives (n = 6/6)	2.893 (5, .716)	1.45	1.31, 1.60
Diesel exhaust grouped (n = 5/5)	2.837 (4, .585)	0.97	0.95, 1.00
By comparison population			
Cohort studies			
Internal controls/occupationally active (n = 6/4)	6.633 (5, .249)	1.48	1.28, 1.70
Regional/state rates (n = 4/3)	26.878 (3, <.001)	1.40	0.83, 2.39
National rates (n = 8/8)	22.270 (7, .002)	1.14	1.00, 1.31
Case–control studies			
Hospital controls (n = 4/3)	2.124 (3, .547)	1.25	1.03, 1.51
Cancer controls (n = 4/3)	8.209 (3, .042)	1.85	1.11, 3.09
General population (n = 3/3)	1.315 (2, .518)	1.05	0.73, 1.50
Internal controls (n = 5/4)	0.086 (4, >.99)	1.49	1.35, 1.64
Multiple sources (n = 4/1)	0.763 (3, .858)	1.59	1.23, 2.06

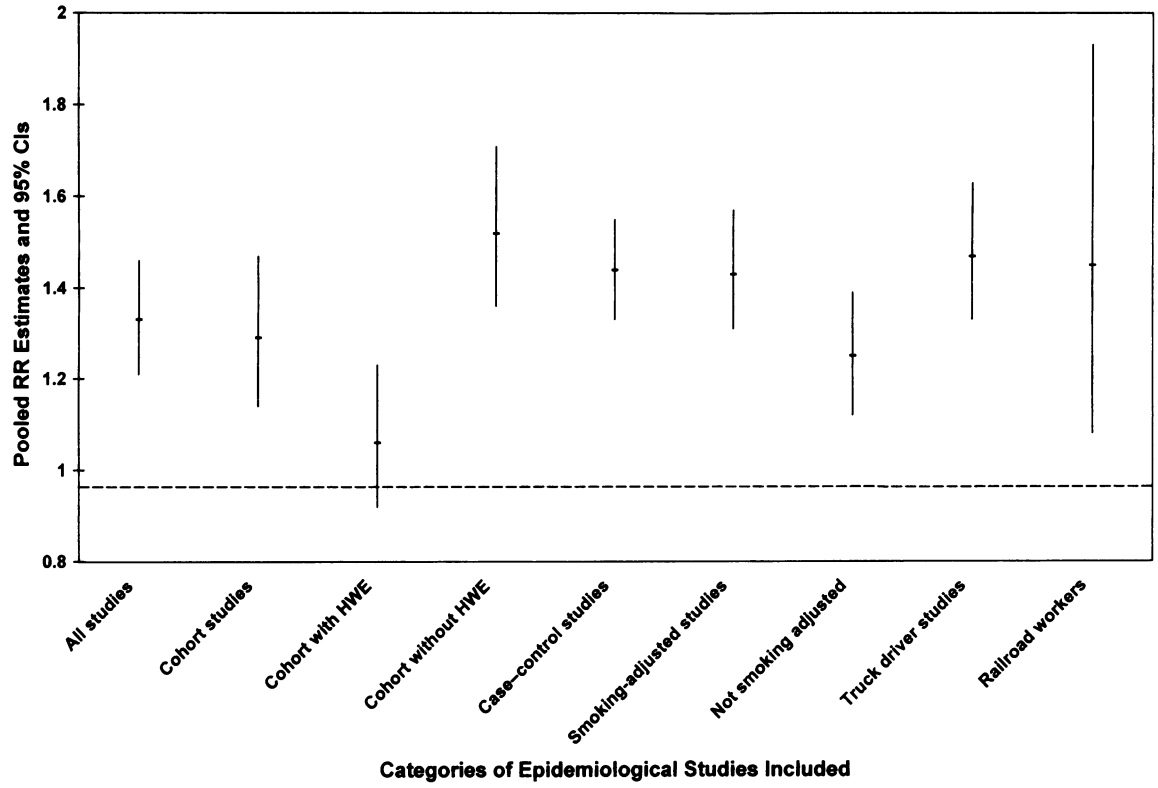
Note. *df* = degrees of freedom; RR = relative risk; CI = confidence interval. Numbers in italics represent values obtained in sensitivity analysis, excluding studies in which exposures to exhaust from diesel versus conventional internal combustion engines could not be easily distinguished (10 estimates from 6 studies were excluded, including Balarajan and MacDowall [1988],[14] Bender et al. [1989],[15] Benhamou et al. [1988] [2 estimates],[16] Buiatti et al. [1985],[17] Hayes et al. [1989] [4 estimates],[33] and Wegman and Peters [1978][54]).

be characterized as a form of confounding, the healthy worker effect is a composite of several processes resulting in selection bias, notably a "healthy hire effect" and a healthy worker survivor effect.[71] Another indirect gauge of selection bias and potential confounding is the apparent influence of the source of the reference population. Studies using an internal or another occupationally active reference population demonstrated a higher pooled risk estimate, and substantially less heterogeneity, than those using regional, state, or national comparison rates.

Exposure misclassification is a problem common to all studies of cancer and diesel emissions. In no case were there direct measurements of historical diesel exhaust exposures of the subjects. In nearly all the investigations, exposure was assigned on the basis of job category (often the usual occupation or job held at retirement), the identification of which is unlikely to be differentially affected by disease status. In general, such nondifferential misclassification will produce a bias toward the null.[72,73] Recall bias in next-of-kin interviews could, however, produce systematic misclassification of exposure to diesel exhaust to the extent that more relatives of lung cancer patients than those of controls considered this exposure to be carcinogenic. However, most interview-based studies assessed diesel exposure indirectly with questions about usual occupation and employment duration, which would not be as susceptible to recall bias as questions specifically addressing exposure to diesel exhaust.

The influence analysis within the occupational subgroups generally had little effect on the magnitude or heterogeneity of the pooled risk estimates, except in the railroad industry. Removing the estimate from the only European railroad study increased the pooled relative risk for railroad workers and substantially decreased heterogeneity.[46] This study included only railroad engineers, did not control for smoking, and relied on comparison with Finnish national mortality rates. Also, Nokso-Koivisto and Pukkala suggested that in both the early and later years of follow-up, there was probably little exposure to diesel exhaust as well as lower cigarette consumption by the study cohort relative to the Finnish population.[46]

Although diesel engines have been used for transportation since the 1930s, their widespread use has occurred primarily since the 1950s, varying by industry and country. For truckers, bus company workers, other professional drivers, and mechanics/garage workers,



Note. CI = confidence interval; HWE = healthy worker effect.

FIGURE 1—Pooled estimates of relative risk (RR) of lung cancer in epidemiological studies involving occupational exposure to diesel exhaust (random-effects models).

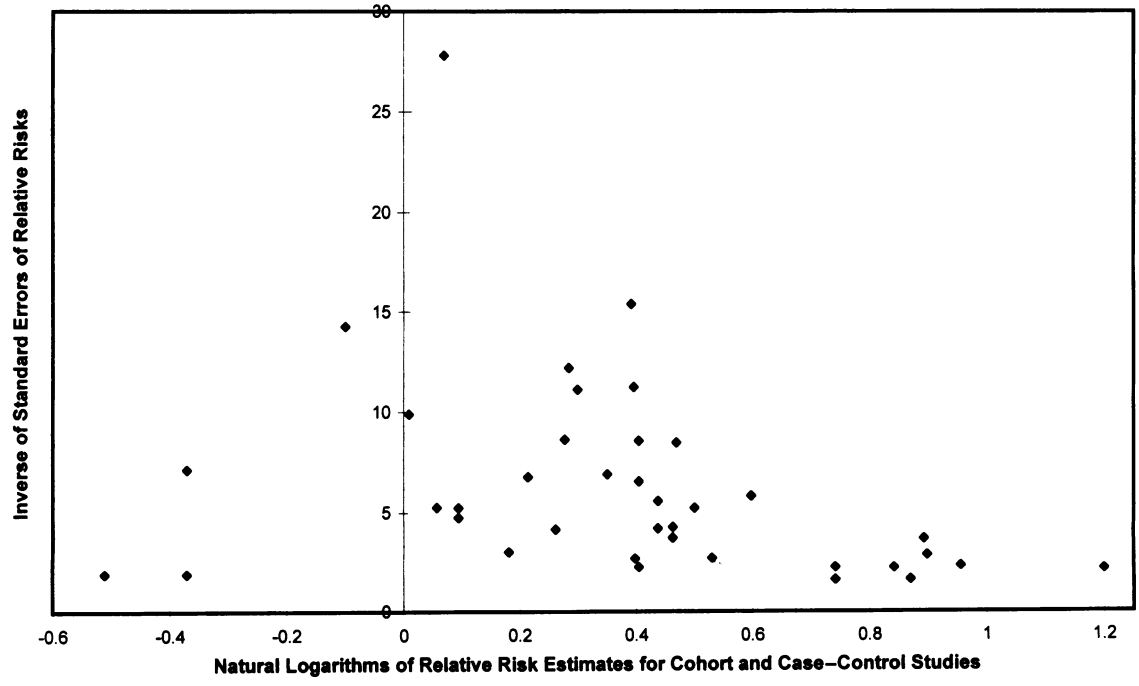


FIGURE 2—Epidemiological studies of occupational exposure to diesel exhaust and lung cancer: funnel plot of natural logarithms of relative risk (RR) estimates vs the inverse of their standard errors (RR for all case–control and cohort studies combined = 0.299).

some of the person-time underlying the risk estimates probably corresponds to exposure to internal combustion engine exhaust. The International Agency for Research on Cancer[1] found gasoline exhaust to be relatively less carcinogenic than diesel exhaust. If this is true, misclassification of exposure to gasoline exhaust as diesel exposure could produce a modest downward bias of the effect estimates in these populations. Excluding studies in which exposures to diesel and conventional internal combustion engine exhaust could not be distinguished resulted in slightly increased risk estimates in several occupational groups, consistent with this notion (Table 3, italicized estimates).

The smoking-adjusted studies showed some evidence of an exposure–response gradient without statistical evidence of heterogeneity. In some individual studies with sufficient sample size and duration of employment data, there were significantly elevated risks associated with the stratum corresponding to the longest duration of employment, including truck drivers,[36,54,55] transportation or heavy equipment operators,[33,59] dock workers,[28] and railroad workers.[29,30,55] The regression analysis was consistent with the existence of a diesel exhaust/lung cancer exposure–response relationship, in that the group of case–control studies in which exposure was equal to or greater than 10 years had a significantly increased metacoefficient relative to the remaining studies.

The case–control metaregression also identified publication year as a source of heterogeneity. Studies published before 1989 had a pooled relative risk of 1.25 (95% CI = 1.10, 1.42), while those published in 1989 or later had a pooled relative risk of 1.53 (95% CI = 1.40, 1.68). Date of publication may serve as a surrogate for study quality or for temporal trends in exposure or disease incidence. However, while more post-1988 studies were of higher quality, the mix of study populations was a more important determinant of the observed differences between the earlier and later studies, with the earlier studies containing more general diesel-exposure studies and the post-1988 group containing more occupation-specific subgroups (3 each of truck drivers and of mechanics/garage workers).

Publication bias is of greater concern in random-effects than fixed-effects models, because the former tend to weight large and small studies more evenly and are therefore more sensitive to the effects of large risk estimates derived from small studies.[74] Figure 2 reveals no systematic relationship between study size and magnitude of risk, although there is a lower density of studies in the lower left, indicating fewer small, statistically insignificant studies. However, many of the investigations in this meta-analysis focused on multiple chemical exposures, adverse health outcomes, or occupations with variable diesel exhaust exposure patterns, so that the relationship between diesel exhaust and lung cancer represented only 1 dimension of these studies. During the course of this analysis, which was conducted as part of a widely publicized government diesel health effects evaluation, only 1 relevant unpublished technical report was brought to our attention—a study on the mortality of US veterans by occupation.[75] Smoking-adjusted relative risks for several diesel-exposed occupations presented in that document are consistent with those reported here. Thus, although publication bias cannot be completely ruled out, it is an unlikely explanation of our findings.

After this report was originally submitted for publication, another meta-analysis of 23 studies of diesel exhaust and lung cancer was published.[76] Bhatia et al. used different study inclusion criteria, used a fixed-effects rather than random-effects model, and presented a number of relative risk estimates around 1.33, most of which contained substantial heterogeneity.[76] Their findings showed, similar to ours, that neither confounding by smoking nor publication bias could explain the consistently increased relative risks for lung cancer observed in diesel-exposed populations. However, they did not attempt to explore systematically the basis for the heterogeneity among studies, stating instead that this could be explained intuitively "from study methods and populations."

Our analysis shows that some sources of heterogeneity, such as adjustment for smoking, could reasonably be intuited; others, such as the presence of a healthy worker effect, are less obvious. For the few subset estimates that Bhatia et al. reported,[76] our corresponding estimates are slightly larger, presumably owing to differences in the risk estimates included and, in some instances, to our use of the random-effects model. Despite these differences, however, our findings are clearly complementary.

We did not construct a formal index to represent study quality, because analysis of study characteristics provides more useful information than subjective quality scores.[74] We found that stratification by several factors that were consistent with higher study quality contributed to higher pooled estimates of risk and lower heterogeneity; these factors included (1) adjustment for confounding by cigarette smoking and other covariates, (2) having a lower likelihood of selection bias and confounding, manifested by both the absence of a healthy worker effect and the use of internal or other occupationally active controls in both cohort and case–control studies, and (3) having more than a minimal number (n = 10) of lung cancer cases in the study.

These quality indicators clearly overlap, however. For example, the use of internal or other occupationally active controls tends to decrease selection bias and confounding underlying the healthy worker effect and to diminish potential effects of confounding by cigarette smoking by creating similar distributions of this confounder in both study and comparison populations. There is suggestive evidence of an exposure–response relationship in smoking-adjusted studies as well. Among studies in which the subjects were most likely to have had substantial exposure to diesel exhaust, the pooled smoking-adjusted relative risk was 1.47 (95% CI = 1.29, 1.67). In summary, this meta-analysis provides quantitative evidence consistent with several prior reviews, which have concluded that the epidemiological evidence supports a causal relationship between occupational exposure to diesel exhaust and lung cancer.[1–3,76] □

Contributors

M. Lipsett and S. Campleman both planned the study, coded and analyzed the data, and wrote the manuscript.

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References

1. International Agency for Research on Cancer (IARC). *Diesel and Gasoline Engine Exhausts and Some Nitroarenes.* Lyon, France: IARC; 1989:1–185. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 46.
2. Cohen AJ, Higgins MWP. Health effects of diesel exhaust: epidemiology. In: *Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects. A Special Report of the Institute's Diesel Working Group.* Cambridge, Mass: Health Effects Institute; April 1995:251–292.
3. *International Programme on Chemical Safety, Diesel Fuel and Exhaust Emissions.* Geneva, Switzerland: World Health Organization; 1996. Environmental Health Criteria 171.
4. Stöber W, Abel UR. Lung cancer due to diesel soot particles in ambient air? A critical appraisal of epidemiological studies addressing this question. *Int Arch Occup Environ Health.* 1996;68(suppl):S3–S61.
5. Muscat JE, Wynder EL. Diesel engine exhaust and lung cancer: an unproven association. *Environ Health Perspect.* 1995;103:812–818.
6. California Office of Environmental Health Hazard Assessment. *Health Effects of Diesel Exhaust.* Sacramento: California Office of Environmental Health Hazard Assessment; 1998.

7. MEDLINE [database online]. Bethesda, Md: National Library of Medicine; 1996.
8. TOXLINE [database online]. Bethesda, Md: National Library of Medicine; 1996.
9. NIOSHTIC [database on CD-ROM]. Cincinnati, Ohio: National Institute of Occupational Safety and Health; 1996.
10. Hertz-Picciotto I, Smith AH, Holtzman D, Lipsett M, Alexeeff G. Synergism between occupational arsenic exposure and smoking in the induction of lung cancer. *Epidemiology.* 1992;3: 23–31.
11. International Agency for Research on Cancer (IARC). *Man-Made Mineral Fibers and Radon.* Lyon, France: IARC; 1988:202–204, 214–228, 233–237. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 43.
12. Chau N, Benamghar L, Pham QT, Teculescu D, Rebstock E, Mur JM. Mortality of iron miners in Lorraine (France): relations between lung function and respiratory symptoms and subsequent mortality. *Br J Ind Med.* 1993;50:1017–1031.
13. Burns PB, Swanson GM. The Occupational Cancer Incidence Surveillance Study (OCISS): risk of lung cancer by usual occupation and industry in the Detroit metropolitan area (Michigan USA). *Am J Ind Med.* 1991;19:655–672.
14. Damber L, Larsson LG. Occupation and male lung cancer: a case-control study in northern Sweden. *Br J Ind Med.* 1987;44:446–453.
15. Lerchen ML, Wiggins CL, Samet JM. Lung cancer and occupation in New Mexico. *J Natl Cancer Inst.* 1987;79:639–645.
16. Ahlberg J, Ahlbom A, Lipping H, Norrel S, Osterblom L. Cancer among professional drivers—a problem-oriented register-based study [Swed]. *Lakartidningen.* 1981;78:1545–1546.
17. Balarajan R, McDowall ME. Professional drivers in London: a mortality study. *Br J Ind Med.* 1988;45:483–486.
18. Bender AP, Parker DL, Johnson RA, et al. Minnesota highway maintenance workers study: cancer mortality. *Am J Ind Med.* 1989;15: 545–556.
19. Benhamou S, Benhamou E, Flamant R. Occupational risk factors of lung cancer in a French case-control study. *Br J Ind Med.* 1988;45: 231–233.
20. Buiatti E, Krievel D, Geddes M, Santucci M, Pucci N. A case-control study of lung cancer in Florence, Italy, I: occupational risk factors. *J Epidemiol Community Health.* 1985;39: 244–250.
21. Boffetta P, Harris RE, Wynder EL. Case-control study on occupational exposure to diesel exhaust and lung cancer risk. *Am J Ind Med.* 1990;17:577–592.
22. Boffetta P, Harris RE, Wynder EL. Diesel exhaust exposure and lung cancer risk. *Exp Pathol.* 1989;37:32–38.
23. Boffetta P, Stellman SD, Garfinkel L. Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. *Am J Ind Med.*1988;14:403–415.
24. Coggon D, Pannett B, Acheson ED. Use of job-exposure matrix in an occupational analysis of lung and bladder cancers on the basis of death certificates. *J Natl Cancer Inst.* 1984;72:61–65.
25. Damber L, Larsson LG. Professional driving, smoking, and lung cancer: a case referent study. *Br J Ind Med.* 1985;42:246–252.
26. Decoufle P, Stanislawczyk K, Houten LH, Bross IDJ, Viadana E. *A Retrospective Survey of Cancer in Relation to Occupation.* Washington, DC: National Institute of Occupational Safety and Health; 1977. DHEW publication 77-178.
27. Edling C, Anjou CG, Axelson O, Kling H. Mortality among personnel exposed to diesel exhaust. *Int Arch Occup Environ Health.* 1987;59:559–565.
28. Emmelin A, Nystrom L, Wall S. Diesel exhaust exposure and smoking: a case reference study of lung cancer among Swedish dock workers. *Epidemiology.* 1993;4:237–244.
29. Garshick E, Schenker MB, Munoz A, et al. A case-control study of lung cancer and diesel exhaust exposure in railroad workers. *Am Rev Respir Dis.* 1987;135:1242–1248.
30. Garshick E, Schenker MB, Munoz A, et al. A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. *Am Rev Respir Dis.* 1988;137:820–825.
31. Guberan E, Usel M, Raymong L, Bolay J, Fioretta G, Puissant J. Increased risk for lung cancer and for cancer of the gastrointestinal tract among Geneva professional drivers. *Br J Ind Med.* 1992;49:337–344.
32. Gustafsson L, Wall S, Larsso LG, Skog B. Mortality and cancer incidence among Swedish dock workers—a retrospective cohort study. *Scand J Work Environ Health.* 1986;12:22–26.
33. Gustavsson P, Plato N, Lidstrom EB, Hogstedt C. Lung cancer and exposure to diesel exhaust among bus garage workers. *Scand J Work Environ Health.* 1990;16:348–354.
34. Hall NEL, Wynder EL. Diesel exhaust exposure and lung cancer: a case-control study. *Environ Res.* 1984;34:77–86
35. Hansen ES. A follow-up study on the mortality of truck drivers. *Am J Ind Med.* 1993;23: 811–821.
36. Hayes RB, Thomas T, Silverman DT, et al. Lung cancer in motor exhaust-related occupations. *Am J Ind Med.* 1989;16:685–695.
37. Howe GR, Fraser D, Lindsay J, Presnal B, Yu SZ. Cancer mortality (1965–77[HA1]) in relation to diesel fume and coal exposure in a cohort of retired railway workers. *J Natl Cancer Inst.* 1983;70:1015–1019.
38. Kaplan I. Relationship of noxious gases to carcinoma of the lung in railroad workers. *JAMA.* 1959;171:2039–2043.
39. Kauppinen TP, Partanen TJ, Hernberg SG, et al. Chemical exposures and respiratory cancer among Finnish woodworkers. *Br J Ind Med.* 1993;50:143–148.
40. Luepker RV, Smith ML. Mortality in unionized truck drivers. *J Occup Med.* 1978;20:677–682.
41. Magnani C, Pannett B, Winter PD, Coggon D. Application of a job-exposure matrix to national mortality statistics for lung cancer. *Br J Ind Med.* 1988;45:70–72.
42. Maizlish N, Beaumont J, Singleton J. Mortality among California highway workers. *Am J Ind Med.* 1988;13:363–379.
43. Menck HR, Henderson BE. Occupational differences in rates of lung cancer. *J Occup Med.* 1976;18:797–801.
44. Milne KL, Sandler DP, Everson RD, Brown SM. Lung cancer and occupation in Alameda County: a death certificate case-control study. *Am J Ind Med.* 1983;4:565–575.
45. Netterström B. Cancer incidence among urban bus drivers in Denmark. *Int Arch Occup Environ Health.* 1988;61:217–221.
46. Nokso-Koivisto P, Pukkala E. Past exposure to asbestos and combustion products and incidence of cancer among Finnish locomotive drivers. *Occup Environ Med.* 1994;51:330–334.
47. Pfluger DH, Minder CE. A mortality study of lung cancer among Swiss professional drivers: accounting for the smoking related fraction by a multivariate approach. *Soz Praventivmed.* 1994;39:372–378.
48. Raffle PAB. The health of the worker. *Br J Ind Med.* 1957;14:73–80.
49. Rafnsson V, Gunnarsdottir H. Mortality among professional drivers. *Scand J Work Environ Health.* 1991;17:312–317.
50. Rushton L, Alderson MR, Nagarajah CR. Epidemiological survey of maintenance workers in London Transport Executive bus garages and Chiswick Works. *Br J Ind Med.* 1983;40: 340–345.
51. Schenker MB, Smith T, Munoz A, Woskie S, Speizer FE. Diesel exposure and mortality among railway workers: results of a pilot study. *Br J Ind Med.* 1984;41:320–327.
52. Siemiatycki J, Gerin SP, Stewart P, Nadon L, Dewar R, Richardson L. Associations between several sites of cancer and ten types of exhaust and combustion products. *Scand J Work Environ Health.* 1988;14:79–90.
53. Siemiatycki J. Discovering occupational carcinogens in population-based case-control studies: review of findings from an exposure-based approach and a methodologic comparison of alternative data collection strategies. *Rec Res Cancer Res.* 1990;120:25–38.
54. Steenland NK, Silverman DT, Hornung RW. Case-control study of lung cancer and truck driving in the Teamsters Union. *Am J Public Health.* 1990;80:670–674.
55. Swanson GM, Lin CS, Burns PB. Diversity in the association between occupation and lung cancer among black and white men. *Cancer Epidemiol Bio Prev.* 1993;2:313–320.
56. Waller RE. Trends in lung cancer in London in relation to exposure to diesel fumes. *Environ Int.* 1981;5:479–483.
57. Wegman DH, Peters JM. Oat cell lung cancer in selected occupations: a case-control study. *J Occup Med.* 1978;20:793–796.
58. Williams RR, Stegens NL, Goldsmith JR. Associations of cancer site and type with occupation and industry from the Third National Cancer Survey Interview. *J Natl Cancer Inst.* 1977;59: 1147–1185.
59. Wong O, Morgan RW, Kheifets L, Larson SR, Whorton MD. Mortality among members of a heavy construction equipment operators union with potential exposure to diesel exhaust emissions. *Br J Ind Med.* 1985;42:435–448.
60. Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev.* 1987;9:1–30.
61. Breslow NE, Day NE. *Statistical Methods in Cancer Research, I: The Analysis Of Case-Control Studies.* Lyon, France: International Agency for Research on Cancer; 1980. Scientific publication no. 32.
62. Checkoway H, Pearce N, Crawford-Brown D. *Research Methods in Occupational Epidemiology.* New York, NY: Oxford University Press; 1989:125–128.
63. Dersimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177–188.
64. Petitti DB. Meta-analysis, decision analysis, and cost-effectiveness analysis. Methods

for quantitative synthesis in medicine. London, England: Oxford University Press; 1994. Monographs in Epidemiology and Biostatistics, Vol. 24.
65. Marshall JR, Hastrup JL. Mismeasurement and the resonance of strong confounders: uncorrelated errors. *Am J Epidemiol.* 1996; 143:1069–1078.
66. Muscat J. Carcinogenic effects of diesel emissions and lung cancer: the epidemiological evidence is not causal. *J Clin Epidemiol.* 1996;49:891–892.
67. Nelson LM, Longstretch WT Jr, Koepsell TD, Checkoway H, van Belle G. Completeness and accuracy of interview data from proxy respondents: demographic, medical, and life-style factors. *Epidemiology.* 1994;5:204–217.
68. Hansen KS. Validity of occupational exposure and smoking data obtained from surviving spouses and colleagues. *Am J Ind Med.* 1996;30:392–397.
69. Axelsson G, Liljeqvist T, Andersson L, Bergman B, Rylander R. Dietary factors and lung cancer among men in west Sweden. *Int J Epidemiol.* 1996;25:32–39.
70. Wynder EL, Miller S. Motor exhaust-related occupations and bladder cancer [letter]. *Cancer Res.* 1988;48:1989–1990.
71. Arrighi HM, Hertz-Picciotto I. The evolving concept of the healthy worker survivor effect. *Epidemiology.* 1994;5:189–196.
72. Dosemici M, Wacholder S, Lubin JH. Does nondifferential misclassification of exposure always bias a true effect toward the null value? *Am J Epidemiol.* 1990;132:746–748.
73. Correa-Villaseñor A, Stewart WF, Franco-Marina F, Seacat H. Bias from nondifferential misclassification in case-control studies with three exposure levels. *Epidemiology.* 1995;6: 276–281.
74. Greenland S. Invited commentary: a critical look at some popular meta-analytic methods. *Am J Epidemiol.* 1994;140:290–296.
75. National Cancer Institute. *Mortality Risks by Occupation Among US Veterans of Known Smoking Status, 1954–1980.* Washington, DC: US Dept of Health and Human Services; 1992. NIH publication 92-3407.
76. Bhatia R, Lopipero P, Smith AH. Diesel exhaust and lung cancer. *Epidemiology.* 1998; 9: 84–91.